

YAWS

RESULTS OF NEOSALVARSAN THERAPY AFTER FIVE YEARS

BY

W. L. MOSS, M.D.

ASSISTANT PROFESSOR OF BACTERIOLOGY AND IMMUNOLOGY,
HARVARD UNIVERSITY MEDICAL SCHOOL, BOSTON, MASS.

(From the Department of Bacteriology and Immunology, Harvard
Medical School)

(Received for publication 6 September, 1926)

At the request of the Military Government of the Dominican Republic the School of Tropical Medicine, Harvard University, sent a commission consisting of Drs. A. W. Sellards, W. L. Moss, and G. H. Bigelow to Santo Domingo during the summer of 1920, to study yaws. The results of the observations made were published in the *John Hopkins Hospital Bulletin* in February, 1922. During the summer of 1925, the writer returned to Santo Domingo for the purpose of observing the results of neosalvarsan therapy after an interval of five years, and collecting such additional data as might be available or of interest in connection with the series of 1,046 cases on which fairly complete records were made in 1920.

To make intelligible this report and for the purpose of comparison, a brief review of the results of the 1920 expedition is necessary.

Framboesia tropica, Yaws, or, as it is called in Santo Domingo, 'Buba' is a specific infectious disease of the tropics, caused by the *Treponema pertenue* (Castellani), characterised by a framboesiform granulomatous eruption.

The course of the disease, like that of syphilis, is usually divided into a primary, secondary, and tertiary stage, but we agree with the majority of authors that yaws and syphilis are separate and distinct diseases, and in our previous report produced evidence which seems adequate to prove the correctness of this view.

It is convenient to make several subdivisions of the secondary stage, especially on account of the large number of patients in Santo Domingo who suffer from the condition of the soles of the feet which they call 'clavus.' Patients with this condition as their only active manifestation of yaws, at the time of observation, made up the largest single group in the series studied, and with the exception of the lesions to which they apply the term 'gomma' (tertiary stage), it produces more pain and disability than any other lesions of the disease.

Our view that clavus is a manifestation of yaws having been called into question, it seems necessary to give the evidence on which we base this view ; this is especially necessary since, as stated above, patients with this condition as their only active manifestation of yaws at the time of observation made up the largest single group in the series studied, 327 cases or 31.2 per cent. Every one of these individuals gave a history of having had the primary lesion and having gone through the florid secondary eruption of granulomata elsewhere on the body, and a great majority of them still bore the typical scars of the preceding lesions. Moreover there were 252 patients, comprising 24 per cent. of the entire series, who presented, in addition to clavus, other well recognised lesions of yaws. The above facts, though highly suggestive, do not exclude the possibility that clavus may be a concomitant, though unrelated, condition. More convincing is the observation of every stage in the development of clavus from typical fresh granulomata on the soles of the feet which later undergo the regressive changes which take place in those located elsewhere on the body, except as modified by the difference in the nature of the surface on which they occur. As the granulomata shrink they separate at the margins from the thick plantar surface and become circumvallate, forming a dry hard core which is the 'nail' from which the condition takes its name ; later the core falls out, leaving a 'nail hole,' a circular 'punched out' opening 0.75 to 1 cm. in diameter with sharp cut edges descending vertically 2 or 3 mm. to a clean flat base ; subsequently, aided perhaps by walking on the bare feet, erosion takes place about the 'nail holes' which extends to meet similar erosions about other holes and gives rise to the peculiar moth-eaten appearance of the soles which is characteristic of the majority of these cases in their later stages. These observations

leave no doubt in our minds that clavus is a manifestation of yaws and that a very great majority of patients, in Santo Domingo at least, develop this condition.

It is convenient to use the same abbreviations as were used in our previous report to designate the various lesions and stages of the disease, and if the reader will take a few moments to familiarise himself with these the understanding of this report will be much facilitated :

- M. Madre buba, mother yaw, or primary lesion.
- B'. Florid secondary eruption of granulomata. Early secondary stage.
- B. Sparse recurring secondary granulomata. Late secondary stage.
- C. Late lesions on the soles. Late secondary stage.
- P. Palmer lesions. Late lesions on the palms. Late secondary stage.
- S.L. Studded Lesions. Late secondary stage (?).
- G. 'Gomma.' Tertiary stage.
- H. History of Yaws. No active lesions present. Quiescent stage.

The term 'studded lesions' was introduced by us to describe a condition which we believe to be a late secondary manifestation of yaws, consisting of moderately hard skin nodules, about 1 cm. in diameter, elevated 3 to 4 mm., not painful, unaccompanied by itching and without striking pigmentary changes until after regression, when an increase of pigmentation may mark their former site. These nodules are thickly studded and regularly set over an area which at first may be not over 8 to 10 cm. in diameter. The size of the area involved may increase to 15 or 20 cm. in diameter by an advancing margin consisting of an almost unbroken row of nodules. As this peripheral advance occurs healing takes place in the centre of the area. In the absence of ulceration retrogression is accompanied by desquamation of epithelium, the nodules gradually flatten out and disappear, leaving no trace, or more often pigmentary changes mark their former site. In no case were the nodules observed to pass through a vesicular stage, but they frequently undergo ulcerative changes probably due to secondary infection.

As pointed out in our previous publication there is much overlapping of the various stages of yaws, an overlapping which far exceeds any which we have observed in syphilis. We think, however, that a very fair idea of the usual sequence of events in yaws may be obtained by arranging the patients observed in 1920 who presented but a single manifestation of the disease (scars excluded) according

to the average age of each group at the time of observation, and comparing this with the average duration of the disease at the same time. This is shown in the following table :

Diagnosis	No. of cases	Average age	Average duration
M	15	6.6 years	2.3 mos
B'	82	8.8 "	12.3 "
B	60	9.3 "	29.6 "
C	327	21.6 "	9 years
H	127	23.8 "	9.7 "
P	5	25 "	14 "
S.L.	37	28.8 "	13.5 "
G	67	29.3 "	16.3 "
	720		

This series comprises 720 cases and the number included in a majority of the groups is large enough to give averages that are probably fairly reliable. This arrangement according to average ages probably indicates the usual sequence in which the various lesions develop. Confirmatory evidence of the correctness of this view is furnished by the fact that the average duration of the disease, at the time of observation in the various groups, with one exception (studded lesions) follows the same orderly progression as do the ages.

The overlapping of the various stages of yaws is well illustrated by a brief recapitulation of some of the tables previously published.

Diagnosis	Number of cases	Diagnosis	Number of cases
M	15	BCP	13
MB'	25	CP	50
B'	82	P	5
MB	6	MG	1
B	60	BG	3
MB'C	13	BCG	2
B'C	24	CG	5
BC	106	CPG	1
C	327	G	67
C+	41	H	55
MBC	5	H+	72

In the above table a plus sign following an abbreviation indicates that there was, in addition to the active manifestation of yaws or the

history of yaws, some other pathological condition present which, in our opinion, was not due to the yaws infection. In a majority of these cases these lesions consisted of old leg ulcers and occurred in the older patients.

Since the observations in 1925 were made largely to determine the late results of the treatment given in 1920 it is necessary, for the purpose of comparison, to review briefly the results of treatment as observed in 1920.

Neosalvarsan was used in the treatment of these cases. The drug was dissolved in freshly distilled water in the proportion of 0.1 gm. to 2 c.c. and injected within thirty to forty-five minutes after being put in solution. The intravenous method was used in all cases except for young children with veins difficult of access, these patients receiving the injections intramuscularly in the buttock. The dose varied from 0.075 gm. for an infant under 1 year of age to 0.6 gm. for a fully developed adult. Intermediate doses were given in proportion to age and body weight. The interval between injections was one week in the majority of cases; exceptionally it was as short as five days and in a moderate number of cases it was ten days to two weeks.

The results were designated as 'cured,' 'practically cured,' 'much improved,' 'improved,' and 'unimproved.' No case was recorded as 'cured,' unless all the lesions (scars excepted) had entirely disappeared. If there remained at the last opportunity of observation only so much as a few black crusts almost ready to fall, where a week or two before there had been an abundant crop of fresh granulomata, such cases were designated as 'practically cured' although we were convinced that could we have seen these patients a week later, without further treatment they would have fallen into the 'cured' list.

Of course it should be understood that the terms 'cured' and 'practically cured' were not intended to express a judgment as to the final result of therapy so recently given but as indicating the disappearance of lesions and freedom from all symptoms of the disease.

In considering the dosage of neosalvarsan that may have produced a given result it seemed better to express it in terms of the number of injections given rather than in absolute amounts of the drug. The reason for this was that the patients varied widely in age and weight and the effort was made to keep the dosage proportional to age and weight.

at that time. There were also excluded from the table thirty-one cases of yaws in which the results of treatment were difficult to determine owing to complicating diseases or for other reasons. Exclusive of these two groups there were 888 cases and on 570 of these there were notes as to the results of treatment.

Owing to the subdivision of these cases into groups according to the several lesions or stages of the disease which they presented, and the smallness of some of these groups, no attempt at detailed analysis of this table seems worth while. Briefly summarised, irrespective of the number of injections each patient received, this table shows the following results :

	Cases	Per cent.
Cured	93	16.32
Practically cured	83	14.56
Much improved	179	31.41
Improved	126	22.10
Unimproved	89	15.61
Total	570	100.00

The results according to the number of injections, irrespective of the stage of the disease, are shown in the following tabulation :

Results	1 Injection, 362 cases		2 Injections, 169 cases		3 Injections, 36 cases		4 Injections, 3 cases	
	Cases	Per cent.	Cases	Per cent.	Cases	Per cent.	Cases	Per cent.
Cured	29	8.0	51	30.2	12	33.3	1	33.3
Practically cured	43	11.8	36	21.3	4	11.1
Much improved	113	31.4	51	30.2	13	36.1	2	66.7
Improved	99	27.3	21	12.4	6	16.6
Unimproved	78	21.5	10	5.9	1	2.9
	362	100.0	169	100.0	36	100.0	3	100.0

These results are very disappointing if one accepts at par the claim which some authors have made, that 90 per cent. of yaws cases are cured by a single injection of salvarsan. It is true that in the above series the final observation was made too soon after the administration of the drug to feel sure that the full effect had manifested itself but, even if the cases recorded as 'cured' are combined with those listed as 'practically cured,' the percentage thus obtained (19.8 per cent.) falls far short of the optimistic claim of 90 per cent. cures after one injection.

Of the 169 patients who received two injections 30.2 per cent. were recorded as 'cured' and 21.3 as 'practically cured.' If we

combine these two groups and consider both as 'cured' the percentage so obtained is 51.5.

The numbers of patients receiving three and four injections are so small that it seems wiser not to attempt to draw conclusions from them.

Admitting that these results are disappointing as measured by the extravagant claims of some authors, we have never seen anything more dramatic in the field of therapy than the prompt disappearance of the loathsome lesions and disabling symptoms of yaws after one or two injections of neosalvarsan.

We have further analysed our 1920 figures to see if they will show what stage of the disease is most readily amenable to treatment. For this purpose it seems probable that more reliable information will be obtained by combining the 'cured' and 'practically cured' cases and considering only those who received a single injection and in whom there was no overlapping of the stages of yaws.

Presented in this way the cases are shown in the following table :

Diagnosis	Total number of cases	Average age in years	No. of cases result noted	Cured or practically cured after 1 injection	
M	15	6.6	11	7	63.63
B'	82	8.8	66	27	40.91
B	60	9.3	36	5	13.88
C	327	21.6	184	8	4.34
P	5	25	2	0	...
S.L.	37	28.8	20	2	10.0
G	67	29.3	43	0	...

The number of cases comprising some of the groups in the above table is too small to be of value for statistical purposes, but taken as a whole the figures seem to show what we would expect, i.e., the earlier the stage of the disease, the more readily does it respond to treatment.

Of the 1,046 cases studied in 1920 we had the opportunity, in 1925, of actually examining 366 and of getting what appeared to be reliable histories of 53 more. Among the latter group there were a number of patients who had died during the epidemics of dysentery and small-pox which visited this section since 1920. Some had died as the result of other diseases or of accidents; others in this group whom we did not actually see and examine sent word by adult members of their families that they were 'cured' and could see no reason for undertaking a long tedious journey on foot or by horse simply to report that they had remained free from signs and symptoms of yaws for five years. In no instance did we include a case unless the history seemed worthy of credence.

We are, therefore, able to report on 419 of the original 1,046 cases, an interval of five years having elapsed between the observations.

Some of the more important data on these cases are summarised in the following table :

Diagnosis	No. of cases			Age in years			Duration in years			No. of injections prior last observation				Results in 1920				Free interval, uncured cases		
	M.	F.	Total	Min.	Max.	Av.	Min.	Max.	Av.	1	2	3	4	unob	uc	pc	c	Min.	Max.	Av.
M	4	1	5	4	18	9'4	1/12	6/12	3/12	3	2	2	2	1	2/12	9/12	11/24
MB'	5	7	12	2	30	10'7	1/12	1	7/12	7	3	2	3	4	3	1/12	4 ⁵ /12	2 ⁷ /12
B'	22	14	36	1 ⁶ /12	30	8'8	2/12	2	9/12	18	14	1	...	3	8	13	12	3/12	4 ¹¹ /12	2 ¹⁰ /12
MB	2	...	2	5	35	20'0	1/12	4/12	5/24	1	...	1	2
B	11	12	23	1	81	12'3	4/12	17	2 ⁴ /12	7	7	1	...	8	6	2	7	3/12	4 ⁹ /12	3 ¹ /12
MB'C	4	2	6	1	23	11'6	3/12	10/12	6/12	3	2	1	2	2	1	4	4 ⁶ /12	4 ³ /12
B'C	5	4	9	2 ⁹ /12	25	14'0	2/12	1 ⁶ /12	8/12	2	6	1	1	4	3	2	4 ¹¹ /12	3 ⁷ /12
MBC	1	...	1	8'0	7/12	...	1	1	4
BC	32	15	47	3	35	15'9	6/12	25	5 ⁹ /12	23	14	10	27	6	4	2/12	4 ¹¹ /12	2 ⁴ /12
C	101	48	149	3	80	23'0	4/12	55	9	65	26	4	1	53	80	6	10	1/12	4 ¹¹ /12	2 ¹⁰ /12
C+	17	4	21	10	60	28'5	1	16	7 ¹¹ /12	9	3	3	...	6	13	...	2	1/12	4 ⁵ /12	1 ¹¹ /12
H	14	16	30	2	50	20'3	6/12	27	6 ¹⁰ /12	25	4	1	1/12	4 ¹¹ /12	2 ⁷ /12	
H+	4	4	8	2	39	19'0	6/12	34	8 ¹⁰ /12	5	2	1	4 ⁹ /12	4 ¹⁰ /12	4 ¹⁰ /24
MB'CP	1	...	1	15'0	1/12	1	1	3
BP	...	2	2	20	30	25'0	6	23	14 ⁶ /12	...	2	1	1
BCP	4	1	5	7	48	28'0	9/12	43	21 ⁶ /12	1	2	2	...	1	2	4 ⁶ /12	4 ⁶ /12	4 ⁶ /12
CP	9	10	19	15	60	35'4	1	55	24 ² /12	10	3	1	...	5	14	1	4 ⁶ /12	2 ² /12
P	1	...	1	15'0	13	1	9/12
SL & SL+	8	5	13	6	80	32'0	4	30	11 ⁷ /12	6	1	2	...	4	7	1	1	1	4 ¹¹ /12	3 ⁷ /12
BG	1	...	1	60'0	40	1	...	1
BCG	1	...	1	12'0	7	...	1	1
CG	...	2	2	15	25	20'0	4	13	8 ⁶ /12	2
G	17	8	25	9	40	25'6	2	38	17 ⁶ /12	12	2	3	1	7	18	5/12	4 ⁷ /12	3 ¹ /12
	264	155	419	198	95	18	3	105	185	42	49	2 ⁹ /12+

unob = unobserved ; uc = uncured ; pc = practically cured ; c = cured.

These various cases have been grouped according to the several lesions of yaws which they presented when first seen in 1920, and the groups are arranged in what we think is approximately their chronological sequence.

As pointed out in our previous publication, a considerable number of cases were seen but once in 1920; most of these came during the last few days of our stay, received a single injection, and there was insufficient time before our departure to observe the results of the treatment; there were 105 such cases among the 419 cases in the 1925 series. There were also included in the 419 cases 38 individuals who, in 1920, gave a history of yaws and received treatment although they presented no active manifestation of the disease at that time. Of the remaining 276 cases, 185 were noted as 'uncured'; 42 as 'practically cured' and 49 as 'cured' at the time of the last observation in 1920. The number of injections which these patients had received prior to the last observation is given in the column just preceding the one headed 'Results in 1920.' It should be noted that a considerable number of the cases in 1920 received an injection at the time of the last observation; this final injection is not recorded in the 'number of injections' column in the above table as it could not have influenced the results as noted in 1920 but it is included in the next table as it may have influenced the results as noted in 1925.

It has already been pointed out that the use of the terms 'cured' and 'practically cured' was not intended to express a final judgment as to the result of therapy in 1920 and even in the case of the 1925 observations the term 'cured' is intended only to express freedom from signs and symptoms of the disease from the time of their disappearance which was at, or very shortly after, the last treatment in 1920, to the date of observation in 1925, i.e., a period of approximately five years.

The promptness with which the primary and secondary lesions of yaws, even such late secondary lesions as clavus, disappear after one or two injections of arsphenamine or its modifications, is familiar to all who have had a sufficient experience with the disease. In our experience the average time is about two weeks. If the lesions in the primary or secondary stage persist a month or longer after treatment and then disappear, we are inclined to regard this as a spontaneous

remission or perhaps a remission influenced to some extent by treatment, but not a cure. In these cases lesions are very apt to recur after a shorter or longer free interval.

We have no data on the length of the free interval which may follow a spontaneous remission in the course of the disease but where any free interval occurred following treatment in 1920 among the cases which we designated as 'uncured' in 1925, we have shown in the above table the minimal, maximal and average free interval for each group. The average free interval for the 195 patients which represents the total uncured group was 2 years 9.6 months, and from the histories obtained we suspect that this is considerably longer than the average free interval following a spontaneous remission.

There were four cases in which cure seemed to have followed treatment in 1920 and a subsequent re-infection occurred. The data on these four cases are presented in the following table.

Serial number	Observations in 1920						Observations in 1925			
	Sex	Age	Diag.	Dur. years	Number injects	Result	Cured after	Free interval	First return lesion	Physical exam.
642	M.	1	MB'C	—1	2	Improved	1 week	Years 4 ⁹ / ₁₂	M	M
472	M.	9	B'	1	2	Cured	...	4 ⁵ / ₁₂	M	M
439	F.	7	B	2	2	Much improved	1 week	3 ⁶ / ₁₂	M	MB
268	M.	8	C	2	1	Unobs.	2 weeks	4 ¹⁰ / ₁₂	M	M

It will be noted that all of these patients were young, that the duration of the disease at the time of the treatment in 1920 had not exceeded two years in any case; that the lesions disappeared promptly after treatment and there ensued a long interval in which they were entirely free from signs and symptoms of yaws and that on examination all presented lesions which strongly suggested the primary lesion and that one patient had secondary granulomata.

In the next table the results of the 1920 observations are compared with those of 1925.

1920

1925

Diagnosis	No. of cases	Uncured. No. of injections				Cured and p.e. No. of injections				Unobserved	Uncured	Cured and p.c.	Per cent. cured & p.c.	Uncured	Cured	Per cent. cured	Uncured. No. of injections					Cured. No. of injections				
		1	2	3	4	1	2	3	4								1	2	3	4	5	1	2	3	4	5
		M	5	1	1	2	1								2	3	...	3	2
	5	1	1	2	1	2	3	60.0	3	2	40.0	...	2	1	2
MB'	12	3	4	3	2	3	7	...	9	3	...	1	8	2	1
B'	36	5	3	13	11	1	...	3	8	25	...	20	16	...	4	13	3	1	11	4
	48	8	3	17	14	1	...	5	11	32	74.4	29	19	39.5	5	21	3	3	12	4
MB	2	1	...	1	2	1	1	1	1
B	23	6	1	7	1	...	8	6	9	...	11	12	...	3	6	2	6	5	1
	25	7	...	1	...	1	7	1	...	8	8	9	53.0	12	13	52.0	3	6	2	1	...	6	6	1
MB'C	6	2	1	2	1	2	3	...	4	2	...	1	3	1	1
B'C	9	1	1	6	1	1	7	...	5	4	...	1	4	3	1
MBC	1	1	1	1
BC	47	20	7	3	7	10	27	10	...	22	25	...	7	12	3	4	17	4
C	149	59	20	1	...	6	6	3	1	53	80	16	...	63	86	...	27	34	2	30	39	16	1	...
C+	21	9	2	2	...	1	1	6	13	2	...	7	14	...	4	2	1	2	7	4	1	...
	233	91	29	3	...	11	23	4	1	71	123	39	24.0	102	131	56.0	40	56	6	36	67	26	2	...
H	30	9	21	...	9	16	4	1
H+	8	5	3	...	4	1	1	1	1
	38	14	24	63.0	13	1	17	5	2
MB'CP	1	1	1	1	1
BP	2	2	2	2	1	1
BCP	5	1	2	2	...	3	...	2	3	...	1	1	1	1	1
CP	19	10	3	1	5	14	5	14	...	2	2	...	1	...	3	8	3
P	1	1	1	1
	28	10	3	1	...	2	4	8	14	6	30.0	9	19	68.0	4	4	...	1	...	4	10	5
SL & SL+	13	6	1	2	4	7	2	...	4	9	...	2	2	2	4	2	1	...
	13	6	1	2	4	7	2	22.0	4	9	69.0	2	2	2	4	2	1	...
BG	1	1	1	1	1
BCG	1	...	1	1	1	1
CG	2	2	2	2
G	25	12	2	3	1	7	18	21	4	...	5	11	2	3	...	2	1	1
	29	12	3	3	2	9	20	22	7	24.0	5	11	2	3	1	4	1	1	...	1
	...	135	40	8	2	33	49	8	1	105	185	91	...	195	224	...	72	103	14	5	1	72	107	41	3	1
	419	185	67%			91	33%			381	419	195	46.5%			224	53.5%				

Attention is again called to the fact that the results in 1925 were recorded in many cases after one more injection of neosalvarsan than the patient had received at the time of recording the results in 1920.

Of the present series of 419 cases, 105 were not observed in 1920 after they had received treatment. In addition to these there are included in this table 38 cases who gave a history of yaws in 1920 but who had no active lesions at the time of observation; they were seen and treated during what we considered to be a period of spontaneous remission, therefore the result of treatment could not be observed at that time. Subtracting these two groups there are left 276 cases of which 185 (67 per cent.) were apparently uncured and 91 (33 per cent.) apparently cured or practically cured.

Of the 419 cases observed in 1925, 195 (46.5 per cent.) remained uncured after five years and 224 (53.5 per cent.) were apparently cured; i.e., they had been free from signs and symptoms of yaws for approximately five years.

A slight error may have been introduced in the above analysis by including the cases who gave a history of having had yaws but presented no active lesions at the time of observation in 1920. That this error cannot be a very material one is evident from the fact that there are only 38 cases in this group and the percentage of 'cures' in this group (63 per cent.) is not greatly in excess of the percentage of cures in the entire series (53.5 per cent.).

The number of cases in some of the groups in the above table are admittedly too small to be of much statistical value but the data are given for what they are worth. In considering the stage to which the disease had progressed it seems logical to denote this stage by the most advanced lesion present; for example, if we group the MB' and the B' cases together there are 48 cases which had reached but not passed the stage of the florid secondary eruption. Similarly if we group all the cases which showed clavus as the most advanced lesion irrespective of the fact that in some of these cases earlier lesions of the disease persisted there are 233 cases which had reached but not passed the clavus stage of the disease.

Tabulated in this way and giving the percentage 'cured' (or 'practically cured') in 1920 and 1925, an interesting tendency to a reversal of these percentages according to the stage of the disease is apparent.

			1920		1925	
			No. of cases	Cured and practically cured	Cured	No. of cases
M	5	60·0	40·0	5
B'	43	74·4	39·5	48
B	17	53·0	52·0	25
C	162	24·0	56·0	233
P	20	30·0	68·0	28
SL	9	22·0	69·0	13
G	20	...	24·0	29

In our previous report on a much larger series of cases the figures seemed to show just what we anticipated they should show, namely, that the earlier the stage of the disease the more amenable it would be to treatment. Observations made five years later on a smaller series seem to indicate that with the exception of the tertiary stage just the reverse of this is true. A much larger series of cases observed over a longer time will be necessary to settle this point.

In this connection it should be pointed out that in the tertiary stage of the disease 'cure' is exceedingly difficult to judge by clinical observation. Many of these patients have been left in a pitiable state of deformity by the ravages of the disease aided, in many cases, by secondary infections. Eyes may have ulcerated out, the nose may have been eaten away, fingers and toes lost, sinuses reaching to the bones may have persisted for years and even though the patient is sterilised as far as his infection with the *treponema pertenuis* is concerned he can never regain the semblance of a sound man.

The 24 per cent. of the 'Gomma' cases recorded as 'cured' were patients whose ulcerations had healed, whose sinuses had ceased to discharge and had closed and who had been free from active signs and symptoms for approximately five years although the evidence of loss of substance and permanent deformities of one sort or another may have persisted. If we had been able to determine the absence of the *treponema* and made this the criterion of cure, the percentage of cures might have been much higher than the figure given for these cases.

In the following table the results as noted in 1920 and 1925 are compared according to the number of injections which the patients had received.

1920								1925									
Uncured				Cured or practically cured				Uncured					Cured				
No. of injections				No. of injections				No. of injections					No. of injections				
1	2	3	4	1	2	3	4	1	2	3	4	5	1	2	3	4	5
				19·6%	55%	50%	33·3%						50%	51%	74·5%	37·5%	50%
135	40	8	2	33	49	8	1	72	103	14	5	1	72	107	41	3	1

Of 168 patients who were observed after one injection in 1920, 33 (19·6 per cent.) were recorded as 'cured' or 'practically cured.' Of 89 patients who were observed after two injections in 1920, 49 (55 per cent.) were recorded 'cured' or 'practically cured.' In 1925, 144 patients were observed who had received one injection in 1920, 210 who had received two injections and 55 who had received three injections; the percentages recorded 'cured' in these three groups are 50 per cent., 51 per cent., and 74·5 per cent. respectively. Owing to the smallness of the numbers in the remaining groups, the percentages obtained for them are probably not significant.

It will be noted that as a result of the observations in 1925 the percentages of 'cures' is practically as great in the group which had received one injection as in that which had received two injections (50 per cent. and 51 per cent.), whereas according to the 1920 observations the number of cures was nearly three times as great in the group which had received two injections (55 per cent.) as in the group which had received one injection (19·6 per cent.). This disproportion is probably to be explained by the fact that the patients who received two injections were observed on an average of about ten days longer after their first injection than patients who had received but one injection.

As far as the above figures are of value they suggest that about 50 per cent. of a miscellaneous series of yaws cases made up of patients in the various stages of the disease, may be cured by a single injection

of neosalvarsan ; that the percentage of cures is not much increased by two injections but is increased considerably by three injections. The final judgment on this point will have to be determined by a larger series of cases than that here reported.

The Wassermann test was done in too few cases to be of any special significance. The data are given, however, as they may be of some value in connection with the reports of other authors.

During the summer of 1920 the Wassermann test was performed on the blood of 91 patients. A strongly positive reaction was obtained in 78 cases (85.7 per cent.), moderately positive in 4 cases, weakly positive in 1 case and negative in 8 cases. The reactions according to the stage of the disease are shown in the following table.

Diagnosis	Strongly Positive	Moderately positive	Weakly positive	Negative
M	2
MB'	1
B'	7	1
B	4	2
B'C	3
BC	5
C	11	1
C+	6	1
H	11	1
H+	4	2	1	1
CP	6
SL	3	1
BG	1
CG	1
SLG	1
G	13	1
Total ...	78	4	1	8

The antigen used was cholesterinized alcoholic extract of human heart muscle, obtained from the Wassermann Laboratory of the Massachusetts State Board of Health. Fresh guinea-pig serum was used as complement, the hemolytic system was immune rabbit serum versus sheep's corpuscles.

In 1925 the Wassermann test was performed on the blood of 73 patients. Blood for this test was taken under sterile precautions, allowed to clot and the serum taken up in sterile glass ampules, hermetically sealed and without refrigeration brought back to the United States, where the tests were performed

in the Wassermann Laboratory of the Massachusetts State Board of Health through the courtesy of Dr. W. A. Hinton, the Assistant Director. The same technique was employed as in 1920 except that the tests were made on serum four to eight weeks old.

The detailed results of the Wassermann tests, together with certain other data, are given in the following table :

1920						1925		1920						1925	
Serial No.	Diagnosis	Duration	Was.	No. of injections	Result	Was.	Result	Serial No.	Diagnosis	Duration	Was.	No. of injections	Result	Was.	Result
866	M	2/12	...	2	i	+	unc	143	C	4	+	2	u	±	unc
306	M	2/12	+	3	mi	-	unc	152	C	1	+	2	mi	+	unc
87	MB'	10/12	...	2	pc	±	unc	162	C	3	...	2	mi	-	unc
113	MB'	4/12	...	2	c	+	c	183	C	5	...	1	unob	+	unc
505	MB'	I	...	2	mi	+	unc	198	C	2	...	2	mi	+	unc
908	MB'	11/12	...	2	mi	+	unc	239	C	3	...	1	unob	±	c
26	B'	8/12	...	2	c	±	unc	268	C	1	unob	+	c
38	B'	8/12	...	2	pc	+	unc	271	C	5	...	1	unob	-	unc
124	B'	8/12	...	2	c	±	unc	313	C	10	+	3	c	-	c
343	B'	2	...	2	pc	-	unc	445	C	25	...	1	unob	+	unc
442	B'	I	...	1	unob	+	unc	482	C	22	...	2	pc	±	unc
906	B'	11/12	...	2	mi	+	unc	520	C	6	...	2	i	±	unc
36	B	6/12	...	2	c	+	unc	538	C	20	...	2	i	-	c
232	B	4	+	0	unob	+	unc	546	C	6	...	1	unob	-	unc
305	B	I	+	2	c	-	c	557	C	9	...	2	i	±	unc
314	B	10	...	2	c	+	unc	778	C	6	...	2	i	+	unc
1136	B	2	...	1	unob	±	unc	907	C	4	...	2	mi	+	unc
660	MB'C	3/12	...	1	unob	±	unc	999	C	11	...	1	unob	-	unc
39	B'C	7/12	...	3	pc	-	c	1138	C	3	...	1	unob	-	c
62	B'C	8/12	+	2	c	-	unc	25	C+	16	...	3	mi	+	unc
58	BC	1 ⁶ /12	+	2	c	-	c	23	H	4	...	1	...	+	unc
167	BC	9	...	3	pc	-	unc	140	H	3	+	2	...	-	c
238	BC	5	...	1	unob	-	unc	233	H	4	+	1	...	+	unc
345	BC	6	...	2	mi	+	unc	451	H	1	...	1	...	-	c
353	BC	5	...	2	i	+	c	948	H	10/12	...	1	...	-	c
405	BC	5	...	2	mi	-	c	552	H+	2	...	3	...	-	c
528	BC	15	...	1	unob	-	unc	905	H+	3	...	1	...	+	unc
657	BC	7	...	1	unob	+	c	68	CP	3	...	2	u	-	unc
670	BC	2	...	2	mi	+	unc	368	CP	22	...	4	i	-	unc
786	BC	2	...	2	mi	-	c	213	SL	20	+	4	pc	±	c
967	BC	5	...	1	unob	+	unc	70	G	2	...	2	i	+	unc
20	C	3	...	1	unob	-	unc	237	G	16	+	4	mi	-	unc
35	C	25	...	3	i	-	unc	596	G	18	...	2	u	+	unc
61	C	4	+	3	mi	+	unc	874	G	24	...	2	u	-	unc
79	C	2	...	1	unob	-	unc	956	G	10	...	2	u	-	c
137	C	3	+	2	i	-	c	1074	G	9	...	1	unob	-	unc
142	C	8	...	2	i	-	unc								

RESULTS :— c = cured ; pc = practically cured ; mi = much improved ; i = improved ;
u = unimproved ; unob = unobserved ; unc = uncured.

The above table shows that of the seventy-three cases on which a Wassermann test was done in 1925 there were only fourteen on which the test was done in 1920. Of these, four gave a positive test both times and all of these were recorded as "uncured" from the history and physical examination made in 1925, before the result of the final Wassermann was known. Two patients gave a positive test in 1920 and a doubtful test in 1925; of these one was recorded as 'cured' and the other as 'uncured.' Eight patients gave a positive test in 1920 and a negative test in 1925. Five of these were recorded as 'cured' and three as 'uncured' as a result of history and physical examination.

If the entire series of seventy-three patients on whom the Wassermann test was performed in 1925 is examined with reference to the results as judged by history and physical examination, the following resumé is obtained from the above table: of twenty-nine cases who gave a positive Wassermann, twenty-five were recorded as 'uncured' and four cases as cured (14 per cent.); of eleven cases who gave a doubtful reaction, nine were recorded 'uncured' and two as 'cured' (18 per cent.); of thirty-three cases who gave a negative reaction, nineteen were recorded as 'uncured' and fourteen as 'cured' (42 per cent.).

That a considerable percentage of negative reactions (58 per cent.) was found in uncured cases five years after insufficient treatment is not surprising.

The fact that four of the twenty-nine cases who gave a positive reaction in 1925, were, as a result of history and physical examination, recorded 'cured' may indicate that our percentage of 'cures' is too high.

RESUMÉ

During the summer of 1920 Drs. Sellards, Bigelow and the author had the opportunity of studying and treating 1,046 cases of yaws occurring in the Dominican Republic.

Neosalvarsan, usually given intravenously, was the therapeutic agent employed. The usual dose for an adult was 0.6 grams. In children the dose was roughly proportioned to age and body weight.

In 570 cases of this series the result of treatment was noted at

times ranging from about one to six weeks after the first injection. Irrespective of the number of injections given there were 176 cases (30.88 per cent.) recorded 'cured' or 'practically cured.' Of 362 cases observed after a single injection, 72 (19.8 per cent.) were recorded as 'cured' or 'practically cured' and of 169 cases observed after two injections, 87 (51.5 per cent.) were recorded as 'cured' or 'practically cured.'

The results of the 1920 observations seemed to indicate that the earlier the stage of the disease the more amenable was it to neosalvarsan therapy.

Of the 1,046 cases studied in 1920, the author had the opportunity of making further observations on 419 during the summer of 1925.

Of these 419 cases 105 were not observed in 1920 after they had received treatment and there are included also 38 cases who gave a history of yaws but who presented no active manifestation of the disease at the time they were observed in 1920. Subtracting these two groups there are left 276 cases, of which 185 (67 per cent.) were apparently uncured and 91 (33 per cent.) recorded as 'cured' or 'practically cured' at the last observation in 1920.

In 1925 observations were made on the 105 cases who escaped observation in 1920 and also on 38 cases who gave only a history of yaws in 1920. Of the entire series of 419 cases, 195 (46.5 per cent.) remained uncured five years after they had received treatment and 224 (53.5 per cent.) had been free from signs or symptoms of yaws for approximately five years.

In analysing the results of the 1925 observations according to the stage of the disease a tendency to a curious reversal of the percentage of 'cures' is noted, namely: that with the exception of the 'gomma' cases, the later stages seem more amenable to neosalvarsan therapy than do the earlier stages. Further observations are necessary to settle this point.

The results as observed five years after treatment suggest that about 50 per cent. of a miscellaneous series of yaws cases made up of patients in the various stages of the disease may be cured by a single injection of neosalvarsan, and that the percentage of cures is not much increased by two injections but is considerably increased by three injections. Before these results can be accepted as establishing a rule a larger series of cases must be studied.

The Wassermann test performed on 91 patients in 1920 gave the following results: strongly positive in 78 cases (85.7 per cent.), moderately positive in 4 cases, weakly positive in 1 case and negative in 8 cases. The 8 negative Wassermanns were given by patients in the late secondary or tertiary stage of the disease.

In 1925 the Wassermann test was done on the blood of 73 patients of whom one did not receive an injection of neosalvarsan in 1920, 23 had received one injection, 38 had received two injections, 8 had received three injections, and 3 had received four injections. Of the 73 patients tested, 29 gave a positive reaction, 4 of whom had been free from symptoms and signs of yaws for approximately five years, 11 gave a doubtful reaction, 2 of whom had been free from symptoms and signs of yaws for approximately five years; 33 gave a negative reaction, 14 of whom had been free from symptoms and signs for a like period.

ACKNOWLEDGMENTS

We are indebted to Mr. H. H. Raymond, President of the Clyde Steamship Company, for his courtesy in extending us free transportation from New York to Santo Domingo and return.

To His Excellency Señor Horacio Vasquez, President of the Dominican Republic, and his Cabinet, we are indebted for many courtesies which facilitated the successful accomplishment of our mission.

Our thanks are due to Señor Santiago Michelena, Jr., Director of the San Luis Sugar Estate, for placing an inspection car at our disposal which saved us much time and wearisome miles of travel by pack train to get across the flooded Yabacao River.

Finally, to Señor M. A. Cocco, Acting Director of Public Works, we are indebted for courtesies too numerous to mention. Had it not been for his interest and assistance the expedition would probably not have been undertaken.